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| EXAMINER | |
|---|---|
| SHEN, WU CHENG WINSTON | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/583,466 | ANDERSON ET AL. | |
| | Examiner | Art Unit | |
| | WU-CHENG Winston SHEN | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *272,273,280-284,288 and 291* is/are pending in the application.

4a) Of the above claim(s) *288* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *272,273,280-284 and 291* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/06/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

Claim amendments filed on 05/07/2010 have been entered.

Claims 1-271, 274-279, 285-287, 289, 290, and 292-386 are cancelled. Claims 272, 281, 288, and 291 are amended.

Claims 272, 273, 280-284, 288, and 291 are pending.

It is noted that that based on election of "retinal abnormalities" recited in claim 280 as elected species encompassed by the elected invention pertaining to "eye abnormality", the amended claim 281 filed on 05/07/2010, being a dependent claim of claim 280 and reciting "a retinal abnormality consistent with vision problems or blindness", is thereby included for examination in this office action. However, the amended claim 288 filed on 05/07/2010 reciting "wherein the eye abnormality comprises optical atropy" is withdrawn from consideration as non-elected species. In this regard, it has been documented on page 19 of the Restriction mailed on 10/14/2009 that various eye abnormalities are different species because each class neurological disease has different underlying cause (etiology), pathological phenotypes, and potential treatments.

Accordingly, claim 288 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 272, 273, 280-284, and 291 are currently under examination to the extent of a phenotype is a retinal abnormality, which is a species belongs to the genus of eye abnormality.

This application 10/583,466 is a 371 of PCT/US04/41721 12/13/2004 which claims benefit of 60/530,043 filed on12/16/2003.

***Claim Objections***

1. Previous objection of claim 273 for being drawn to a non-elected invention since Applicants have elected "eye abnormality" as the phenotype associated with a disruption of a gene which encodes for a PRO0224 recited in claim 273, is ***withdrawn*** because claim 273 filed on 05/07/2010 has been amended to recite "wherein said phenotype comprising an eye abnormality".

2. Claim 273 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

The limitation "an eye abnormality" recited in claim 273 is not further limiting claim 272 because the same limitation is recited in amended claim 272.

3. Claim 272 is objected to because of the following informalities: Lines 2 and 14 of claim 272 recite "PR0224" whereas line 5 of claim 272 recites "PRO224". It appears that "PR0224" recited in lines 2 and 14 of claim 272 should be "PRO224", assuming that "PRO" stands for protein. Appropriate correction is required.

***Claim Rejection - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

4. Previous rejection of claims 272, 273, 280, 282-284, and 291 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps, is ***withdrawn*** because claim 272 has been amended. See MPEP § 2172.01.

Amended claim 272 filed on 05/07/2010 reads as follows: A method of identifying an agent that modulates a phenotype associated with a disruption of the gene that encodes for a native sequence PRO224 polypeptide, wherein said phenotype comprises an eye abnormality, the method comprising: (a) providing a non-human transgenic mammal whose genome comprises a disruption of the gene which encodes for the native sequence PRO224 polypeptide; (b) measuring a physiological characteristic of an eye of the non-human transgenic mammal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of an eye of the non-human transgenic animal mammal that differs from the physiological characteristic of the wild-type mammal is identified as a phenotype resulting from the gene disruption in the non-human transgenic mammal; (d) administering a test agent to the non-human transgenic animal mammal of (a); and (e) determining whether the test agent modulates said phenotype associated with gene disruption in the non-human transgenic animal mammal, whereby an agent which is determined to modulate an eye abnormalit3r associated with a disruption of the gene that encodes for the native sequence PRO224 polypeptide is identified.

5. Claims 272, 273, 280-284, and 291 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments filed on 05/07/2010.*

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

In the present instance, claim 272 recites the broad recitation “a phenotype” in line 9, step(c), and the claim also recites “an eye abnormality” in line 13, step (e) which is the narrower statement of the range/limitation.

Claims 273, 280-284, and 291 depend from claim 272.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

***Written description***

6. Claims 272, 273, 280-284, and 291 remain/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's arguments filed 05/07/2010 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 7-10 of the office action mailed on 01/06/2010. *The inclusion of claim 281 in this maintained rejection is necessitated claim amendments filed on 05/07/2010.*

For the clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 7-10 of the office action mailed on 01/06/2010, is reiterated below, with revisions addressing claim amendments filed on 05/07/2010.

The claims are directed to a method of identifying an agent that modulates a phenotype associated with a disruption of the gene that encodes for a native sequence PRO224 polypeptide, wherein said phenotype comprises an eye abnormality, the method comprising: (a) providing a non-human transgenic mammal whose genome comprises a disruption of the gene which encodes for the native sequence PRO224 polypeptide; (b) measuring a physiological characteristic of an eye of the non-human transgenic mammal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of an eye of the non-human transgenic animal mammal that differs from the physiological characteristic of the wild-type mammal is identified as a phenotype resulting from the gene disruption in the non-human transgenic mammal; (d) administering a test agent to the non-human transgenic animal mammal of (a); and (e) determining whether the test agent modulates said phenotype associated with gene disruption in the non-human transgenic animal mammal, whereby an agent which is determined to modulate an eye abnormalit3r

associated with a disruption of the gene that encodes for the native sequence PRO224 polypeptide is identified.

The nucleotide sequences that encode for native PRO224 polypeptide and variants encompassed within the genus of "the gene that encodes for a native sequence PR0224 polypeptide" of non-human mammal have not been disclosed. Based upon the prior art there is expected to be variation among the species of cDNA, which encode PRO224 polypeptide, because the sequence of PRO224 cDNAs would be expected to vary among individual mammal. The specification discloses isolation of a nucleotide sequence (SEQ ID NO: 1) that encodes a human PR0224 polypeptide (SEQ ID No: 2) from an unknown human cell type (See paragraphs [0230], SEQ ID No: 1 and SEQ ID No: 2, US 2007/0292438, publication of instant application). However, SEQ ID No: 1 is not encompassed by the limitation "gene that encodes for a native sequence PR0224 polypeptide" in the context of disruption of said gene in a transgenic non-human mammal.

The specification discloses that in knockout experiments in mice, the gene encoding PRO224 polypeptides (designated as DNA33221-1133) [UNQ198] was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_019421 or *Mus musculus* hypothetical protein 425018-1, protein reference: NP_062294 or hypothetical protein 425018-1; putative VLDL lipoprotein receptor precursor; DNA segment, Chr 17, ERATO Doi 716, expressed [*Mus musculus*]; the human gene sequence reference: BC007083 or *Homo sapiens*, 8D6 antigen, clone MGC: 14623 IMAGE: 4076237; the human protein sequence corresponds to reference: NP_057663 or 8D6 antigen

(*Homo sapiens*) (See paragraphs [0699] and [0700], US 2007/0292438, publication of instant application). The specification does not provide any information pertaining to the *structure-function relationship* between mouse DNA33221-1133 (UNQ198), SEQ ID NO: 1 (which encodes human PRO224 cDNA), and any other gene encoding a native PRO224 polypeptide encompassed by the genus of the gene that encodes for a native PRO224 polypeptide. There is no evidence on the record of a relationship between the structures of mouse DNA33221-1133 (UNQ198) and SEQ ID NO: 1 cDNA that would provide any reliable information about the structure of other DNAs encoding a native PRO224 polypeptide within the genus. There is no evidence on the record that the mouse DNA33221-1133 (UNQ198) had a known structural relationship to any other gene encoding a native PRO224 polypeptide; the specification discloses only a single mouse DNA33221-1133 (UNQ198) obtained from an undisclosed origin of mouse cells; the art indicated that there is variation between a given polypeptide cDNA sequences and their functions. The specification has not even disclosed the function of mouse DNA33221-1133 (UNQ198) that encodes. There is no evidence of record that would indicate that any of the claimed variants of mouse DNA33221-1133 (UNQ198), even have the biological activity of a native PRO224 polypeptide. In the absence of a functional assay it would not be possible to test variants of the claimed sequences for biological activity of a native PRO224 polypeptide encoded by a gene. In fact, the specification does not disclose any function and/or domain structure of PRO224 polypeptide encoded by mouse DNA33221-1133 (UNQ198). Also with regard to the claimed allelic variants, the skilled artisan cannot envision the structure of such a variant because such variants are randomly produced in nature, and cannot be predicted from a known sequence. The specification does not teach any characteristics of an "allelic" variant that

would distinguish it from a non-natural variant constructed by the hand of man. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus, because a mouse DNA33221-1133 (UNQ198) is not representative of the claimed genus. Consequently, since Applicant was in possession of only the mouse DNA33221-1133 (UNQ198) and since the art recognized variation among the species of the genus of "the gene that encodes for a native sequence PR0224 polypeptide" of non-human mammal, the mouse DNA33221-1133 (UNQ198) was not representative of the claimed genus. Therefore, Applicant was not in possession of the genus of "the gene that encodes for a native sequence PR0224 polypeptide" of non-human mammal as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

***Applicant's arguments***

Applicant argues that Applicants disclose the nucleic acid and amino acid sequence of full-length native sequence PRO224 (see, e.g., Figures 1 and 2, SEQ ID NOs: 1 and 2). Applicants further disclose methods of isolating DNA (see, e.g., pages 106-107, and 1121); methods utilizing non-human homologs of PRO224 (page 116, line 21 to page 117, line 27); and experimental methods and results preparing and using human PRO224 (page 146, line 7 to page 147 line 11) and PRO224 knock-out mice (page 162, line 18 to page 164, line 20). Thus, Applicants disclose sequences and methods used with human and mouse, and which are useful for other animals as well. Applicant argues that since the claim is directed to the gene which encodes for a native sequence PRO224 polypeptide, and since the rejection is directed to an alleged lack of written description for nucleotide sequences that encode all PRO224, variants,

and fragments thereof encompassed within the genus of a gene which encodes for a PRO224 polypeptide, Applicants submit that the rejection is overcome (See page 6 of Applicant's remarks file don 04/06/2010).

***Response to Applicant's arguments***

It is noted that as stated in the maintained rejection, SEQ ID No:1 encodes SEQ ID No:2 (human PRO224 polypeptide) is outside the scope of the genus "the gene that encodes for a native sequence PR0224 polypeptide" of non-human transgenic mammal because a human gene is not present in a non-human animal and cannot be disrupted in a non-human transgenic mammal. The Examiner acknowledges that PRO224 polypeptide encoded by mouse DNA33221-1133 (UNQ198) is disclosed in the specification. However, this written description is maintained because the specification does not provide any information pertaining to the ***structure-function relationship*** between mouse DNA33221-1133 (UNQ198), SEQ ID NO: 1 (which encodes human PRO224 cDNA), and any other gene encoding a native PRO224 polypeptide encompassed by the genus of the gene that encodes for a native PRO224 polypeptide. In fact, the specification does not disclose any function and/or domain structure of PRO224 polypeptide encoded by mouse DNA33221-1133 (UNQ198). There is no evidence of record that would indicate that any of the claimed variants of mouse DNA33221-1133 (UNQ198), even have the biological activity of a native PRO224 polypeptide. In the absence of a functional assay for claimed genus encoding "PRO224 polypeptide", it would not be possible to test variants (e.g. variants due to alternative splicing) and homologs of the claimed genus of sequences for biological activity of a native PRO224 polypeptide encoded by a mammalian gene.

***Enablement***

7. Claims 272, 273, 280-284, and 291 remain/are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. Applicant's arguments filed 05/07/2010 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 10-17 of the office action mailed on 01/06/2010. *The inclusion of claim 281 in this maintained rejection is necessitated claim amendments filed on 05/07/2010.*

For the clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 10-17 of the office action mailed on 01/06/2010, is reiterated below, with revisions addressing claim amendments filed on 05/07/2010.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The nature of the invention is directed to a method of identifying an agent that modulates a phenotype associated with a disruption of the gene that encodes for a native sequence PRO224 polypeptide, wherein said phenotype comprises an eye abnormality, the method comprising: (a)

providing a non-human transgenic mammal whose genome comprises a disruption of the gene which encodes for the native sequence PRO224 polypeptide; (b) measuring a physiological characteristic of an eye of the non-human transgenic mammal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of an eye of the non-human transgenic animal mammal that differs from the physiological characteristic of the wild-type mammal is identified as a phenotype resulting from the gene disruption in the non-human transgenic mammal; (d) administering a test agent to the non-human transgenic animal mammal of (a); and (e) determining whether the test agent modulates said phenotype associated with gene disruption in the non-human transgenic animal mammal, whereby an agent which is determined to modulate an eye abnormalit3r associated with a disruption of the gene that encodes for the native sequence PRO224 polypeptide is identified.

The breadth of the invention encompasses a method of identifying an agent that modulates a phenotype associated with a disruption of the gene that encodes for a native sequence PRO224 polypeptide, wherein said phenotype comprises an eye abnormality, the method comprising: (a) providing any non-human transgenic mammal whose genome comprises a disruption of the gene which encodes for the native sequence PRO224 polypeptide; (b) measuring any physiological characteristic of an eye of the non-human transgenic mammal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of an eye of the non-human transgenic animal mammal that differs from the physiological characteristic of the wild-type mammal is identified as any phenotype resulting from the gene disruption in the non-human transgenic

mammal; (d) administering a test agent to the non-human transgenic animal mammal of (a); and (e) determining whether the test agent modulates said phenotype associated with gene disruption in the non-human transgenic animal mammal, whereby an agent which is determined to modulate an eye abnormalit3r associated with a disruption of the gene that encodes for the native sequence PRO224 polypeptide is identified.

With regard to any non-human transgenic animal, the specification discloses isolation of a nucleotide sequence (SEQ ID NO: 1) that encodes a human PR0224 polypeptide (SEQ ID No: 2) from an unknown human cell type (See paragraphs [0230], US 2007/0292438, publication of instant application). In this regard, it is noted that the human PRO224 cDNA (SEQ ID No: 1) cannot be disrupted in a non-human transgenic animal because the human gene is not present in the genome of a non-human transgenic animal. The specification does not disclose any information regarding the presence of human PRO224 cDNA in the genome of any non-human transgenic animal, which may be then disrupted as required by the claimed methods. With regard to transgene integration, the art taught that the site of integration is uncontrolled and yet is critical due to the possibility of integration into a silent locus. The site of integration may also result in altered tissue specificity, although the promoter used behaves differently at its normal chromosomal localization, with neighboring regulatory elements potentially influencing the transcriptional activity of the transgene (See pg. 159 col. 1 parag. 3, lines 1-7, **Ristevski**, Making better transgenic models: conditional, temporal, and spatial approaches. *Mol Biotechnol.* 29(2): 153-63, 2005). This is known as chromosomal position effects, where host sequences surrounding the site of transgene integration could alter the expected expression pattern, turning

it ectopic or not detectable (See pg 39, col. 1, **Montoliu**, Gene transfer strategies in animal transgenesis. *Cloning Stem Cells.* 4(1): 39-46, 2002).

Furthermore, the status of art indicates that generation of non-human transgenic animal is unpredictable. With regard to mammalian ES cells, it is important to note that **Clark (1998)** clearly discloses that, in principle, then, ES cells would seem the ideal candidate from which to develop an alternative route to transgenesis in live stock. However, despite intensive efforts, no validated ES cells other than mouse ES cells (i.e., cells that will contribute to the germline) have been described for any species of livestock (See right column, page 339, Clark et al., The mammary gland as a bioreactor: expression, processing, and production of recombinant proteins, *J Mammary Gland Biol Neoplasia.* 3(3):337-50, 1998). Consistent with the notion regarding unpredictability of gene targeting in mammalian ES cells other than mouse ES cells, **Williams (2003)** states that "While it has been suggested that a better understanding of the properties of embryonic stem cells could be achieved by work in the mouse and other animals, it is already clear that there are many differences between species in the properties of these cells" (See middle column, page R210, Williams, Death of Dolly marks cloning milestone, *Curr Biol.* 13(6):R209-10, 2003). At the time of filing, the art teaches that the only known non-human animal in which ES cells can be obtained was for mouse. This is because mice are the only mammals in which ES cells can be generated and which chimerism from ES cells extend to the germline (See abstract and page 2, 2nd col., 1st paragraph under "The need for nuclear transfer", **Denning et al**, New frontiers in gene targeting and cloning: success, application and challenges in domestic animals and human embryonic stem cells. 2003, *Reproduction* 126: 1-11, 2003).

With regard to any phenotype and/or any physiological characteristic of an eye of a transgenic mouse, the specification discloses that in knockout mouse experiments, the mouse gene encoding PRO224 polypeptides (designated as DNA33221-1133) [UNQ198] was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_019421 or *Mus musculus* hypothetical protein 425018-1, protein reference: NP_062294 or hypothetical protein 425018-1; putative VLDL lipoprotein receptor precursor; DNA segment, Chr 17, ERATO Doi 716, expressed [*Mus musculus*]; the human gene sequence reference: BC007083 or *Homo sapiens*, 8D6 antigen, clone MGC: 14623 IMAGE: 4076237; the human protein sequence corresponds to reference: NP_057663 or 8D6 antigen (*Homo sapiens*) (See paragraphs [0669] and [0700], US 2007/0292438, publication of instant application). The specification discloses phenotypic Analysis (for Disrupted Gene: DNA33221-1133 (UNQ198) as follows: Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Optic fundus photography was performed on conscious animals using a Kowa Genesis small animal fundus camera modified according to Hawes and coauthors (Hawes et al., 1999 Molecular Vision 1999; 5:22). Intra-peritoneal injection of fluorescein permitted the acquisition of direct light fundus images and fluorescent angiograms for each examination. In addition to direct opthalmological changes, this test can detect retinal changes associated with systemic diseases such as diabetes and atherosclerosis or other retinal abnormalities. Pictures were provided of the optic fundus under normal light. The angiographic pictures allowed examination of the arteries and veins of the eye. In addition an artery to vein (A/V) ratio was determined for the eye (See paragraphs [0708], US 2007/0292438, publication of instant application). Ophthalmology analysis was performed on generated F2 wild type,

heterozygous, and homozygous mutant progeny using the protocol described above. Specifically, the A/V ratio was measured and calculated according to the fundus images with Kowa COMIT+ software. This test takes color photographs through a dilated pupil: the images help in detecting and classifying many diseases. The artery to vein ratio (A/V) is the ratio of the artery diameter to the vein diameter (measured before the bifurcation of the vessels). The specification states that many diseases will influence the ratio, i.e., diabetes, cardiovascular disorders, papilledema, optic atrophy or other eye abnormalities such as retinal degeneration (known as retinitis pigmentosa) or retinal dysplasia, vision problems or blindness. Thus, phenotypic observations which result in an increased artery-to-vein ratio in homozygous (-/-) and heterozygous (+/-) mutant progeny compared to wildtype (+/+) littermates would be indicative of such pathological conditions (See paragraphs [0709], US 2007/0292438, publication of instant application). The specification discloses the Results as follow: In this study, *the (-/-) and (+/-) mice exhibited an increased mean artery-to-vein (A/V) ratio when compared with their (+/+) littermates indicating retinal degeneration*. The specification states that, in summary, by knocking out the gene identified as DNA33221-1133 encoding PRO224 polypeptides, both heterozygous and homozygous mutant progeny exhibit phenotypes which are associated with retinal degeneration. Such detected retinal changes are most commonly associated with cardiovascular systemic diseases or disorders that may be related to the vascular disease of hypertension (and any disease that causes hypertension, e.g. atherosclerosis), diabetes or other ocular diseases corresponding to opthalmological disorders such as retinal degeneration. Thus, antagonists of PRO224 encoding genes would lead to similar pathological retinal changes, whereas agonists would be useful as therapeutic agents in the treatment of hypertension,

atherosclerosis or other opthamological disorders including retinal degeneration and diseases associated with this condition (as indicated above) (See paragraphs [0710], Example 18, US 2007/0292438, publication of instant application).

It is worth noting that the claimed methods require "identifying an agent that modulates a phenotype associated with disruption of the gene that encodes for a PRO224". However, the specification does not provide any information regarding any agent that can reverse/modulate the increased mean artery-to-vein (A/V) ratio when compared with their (+/+) littermates exhibited by the (-/-) and (+/-) mice, which Applicant asserts to be an indication of and/or associated with retinal degeneration. Pertaining to this issue, it is worth noting that the status of art indicates that there is no clear association, as Applicant asserts, between a phenotype of retinal abnormality (retinal degeneration) and a physiological characteristic of increased mean artery-to-vein (A/V) ratio. In this regard, **Upton et al.** teaches retinal abnormalities observed in 5-$HT_{1B}$ knockout, serotonin transporter knockout, serotonin transporter/5-$HT_{1B}$ double knockout and monoamine oxidase A/5-$HT_{1B}$ double knockout mice (See abstract, Upton et al., Lack of 5-$HT_{1B}$ receptor and of serotonin transporter have different effects on the segregation of retinal axons in the lateral geniculate nucleus compared to the superior colliculus, *Neuroscience*, 111(3):597-610, 2002). Upton et al. does not disclose any association between retinal abnormality and increased mean artery-to-vein (A/V) ratio. Furthermore, as discussed in the rejection under 35 U.S.C 112 second, the steps of claim 272 recites two distinct scopes of phenotypes (an eye abnormality in lines 3 and 13 of claim 272, and a phenotype in line 9 of claim 272) of claimed non-human animal that has been modulated by a agent to be identified by the claimed methods.

Furthermore, the status of art at the time of filing as well as at present indicates that the phenotype of transgenic animal, including transgenic mouse, is unpredictable. **Matthaei** teaches that although genetic manipulations in mice have provided a powerful tool for investigating gene function *in vivo*, recent studies have uncovered a number of developmental phenomena that complicate the attribution of phenotype to the specific genetic change. Matthaei further teaches further complications in interpretation due to unexpected epigenetic effects involving transfer of RNA or protein in oocytes or sperm (See abstract, Matthaei, Genetically manipulated mice: a powerful tool with unsuspected caveats. *J Physiol.* 582(Pt 2):481-8, 2007). Matthaei teaches that the site at which the DNA is integrated is random, as are the number of copies of the transgene. Although the expression of the construct is faithful for the promoter, on many occasions it may also be significantly influenced by the local environment at the integration site (the 'position' effect). This can lead to the promiscuous expression of the transgene (often referred to as 'leakiness'), due to modification of the specificity of the promoter, or at times to a more severe phenotype, due to disruption of an unknown gene by insertion of the transgene (insertional mutagenesis). Furthermore, Matthaei teaches that a number of different 'founder' animals with different copy numbers and different integration sites must therefore be assessed in order to determine the correct/faithful expression of each transgene, and surprisingly, in one example, 24 different founders resulted in 24 different expression patterns making it impossible to determine which pattern was correct (See right column, page 481, *J Physiol.* 582(Pt 2):481-8, 2007).

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform

undue experimentation to make and use the claimed invention as recited in claims 272, 273, 280-284, and 291.

***Applicant's arguments Response to Applicant's arguments***

**(i)** Applicants argues that particular sequences, SEQ ID NO: 1 and SEQ ID NO: 2, are disclosed in the application; that the methods recite mammals comprising a disruption of the gene that encodes for a native sequence PR0224 polypeptide, which sequences are provided; that the claimed methods require knock-out mammals with a phenotype comprising an eye abnormality, as disclosed in the application; and that methods for generating such knock-out mammals, and for measuring eye abnormalities, are taught in the application. Thus, Applicants argues that the teaching of the application is sufficient to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation (See pages 7-8 of Applicant's remarks filed on 04/06/2010).

Applicant argues that measurements of artery and vein dimensions or properties, in the retina, which differ between knock-out and wild type mammals, are by definition directed to eye abnormality, as in such a case, the eyes of knock-out mammals differ from the eyes of wild-type mammals. Thus, Applicants believe the USPTO's concerns regarding the association between retinal abnormality and increased mean artery-to-vein ratio are overcome (See page 9of Applicant's remarks filed on 04/06/2010).

*In response*, it is noted that the human PRO224 cDNA (SEQ ID No: 1) cannot be disrupted in a non-human transgenic animal because the human gene is not present in the genome of a non-human transgenic animal. The specification does not disclose any information regarding the presence of human PRO224 cDNA in the genome of any non-human transgenic animal, which may be then disrupted as required by the claimed methods.

With regard to the phenotype, there are two issues. First, the steps of claim 272 recites two distinct scopes of phenotypes (an eye abnormality in lines 3 and 13 of claim 272, and a phenotype in line 9 of claim 272) of claimed non-human animal that has been modulated by a agent to be identified by the claimed methods. Second, the specification and the status of art

(e.g. Upton et al., *Neuroscience*, 111(3):597-610, 2002), does not provide enabling support regarding any agent, or any agonists of PRO224 polypeptide, that can reverse/modulate the increased mean artery-to-vein (A/V) ratio when compared with their (+/+) littermates exhibited by the (-/-) and (+/-) mice, which Applicant asserts to be an indication of and/or associated with retinal degeneration. This issue is relevant to the maintained written description rejection regarding the specification does not provide any information pertaining to the *structure-function relationship* of any native PRO224 polypeptide encoded by a mammalian gene.

**(ii)** Applicant states that much of the discussion on pages 12-13 of the instant Office Action is directed to scientific literature related to transgenic mice, embryonic stem cell methods, and is cited to suggest that the generation of a non-human transgenic animal is allegedly unpredictable. Applicants argues that the present application, and, for example, the Clark, Montoliu, and Ristevski references cited by the USPTO, discuss methods for generating transgenic mammals which do not utilize embryonic stem cells, so that the concerns discussed by the USPTO regarding embryonic stem ceil methods may not apply to all methods of generating transgenic mammals. Moreover, as discussed previously, Applicant argues that the present application discloses the generation of non-human transgenic mice having a disruption in the gene that encoded the PRO 184, and provides detailed methods and teaching regarding the generation and use of these mammals (see, e.g., page 162, line l 8 to page 164, line 20). In particular, the present application not only discloses the methods that were used by the inventors to produce such mammals, but disclose methods for measuring physiological characteristics of an eye of such mammals, as well as presenting the results of such measurements on transgenic mice produced by these methods. Thus, Applicants argues that despite the scientific literature cited to suggest that such methods might be unpredictable, Applicants provide sufficient teaching and experimental results as to teach one of skill in the art how to practice the claimed invention without undue experimentation. Even in view of the concerns raised by the USPTO, the teaching and experimental results provided in the application, in view of the skill and knowledge of one of ordinary skill in the art, is sufficient to enable the practice of the claimed invention without undue experimentation (See page 8 of Applicant's remarks filed on 04/06/2010).

*In response*, the Examiner acknowledges that the specification does provide information regarding knock out PRO224 encoding gene in mice. However, there are two issues with regard to the phenotype cited in claim 272, which has been elaborated in the response **(i)** above.

With regard to the arguments that the Clark, Montoliu, and Ristevski references cited by the USPTO, discuss methods for generating transgenic mammals which do not utilize embryonic stem cells, thereby the claimed methods are enabled. This argument is found not persuasive because alternative methods for generation of a transgenic mammal require "nuclear transfer" technique which was used to create "Dolly" sheep, which is not considered as routine experimentation. With regard to unpredictability of "nuclear transfer", Williams (2003) clearly states that "Animal cloning is already known as an unreliable and risky procedure. It took 276 unsuccessful attempts before Dolly was produced. Many of cloned animals which are carried to term die shortly after birth and suffer deformities. The University of Mossouri team implanted 3,000 embryo in 28 surrogates sows to get just seven piglets" (See left column, page R210, Williams, Death of Dolly marks cloning milestone, *Curr Biol.* 13(6):R209-10, 2003). Therefore, undue experimentation is certainly required for generation of a transgenic mammal via "nuclear transfer" technique.

**(iii)** Applicant states that the USPTO stated that step (e) of claim 272 does not relate back (page 6 of the instant Office Action); however, as amended, Applicants note that step (e) of claim 272 relates back to the phenotype (eye abnormality), and recites "whereby an agent which is determined to modulate an eye abnormality associated with a disruption of the gone that encodes for the native sequence PR0224 polypeptide is identified." (See pages 8-9 of Applicant's remarks filed on 04/06/2010).

*In response*, the Examiner acknowledges that previous rejection of claims 272, 273, 280, 282-284, and 291 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps, has been *withdrawn* in this office action. However, as noted in the response **(i)** above, the specification and the status of art (e.g. Upton et al., *Neuroscience*, 111(3):597-610, 2002) does not provide enabling support regarding any agent, or any agonists of PRO224 polypeptide, that can reverse/modulate the

increased mean artery-to-vein (A/V) ratio when compared with their (+/+) littermates exhibited by the (-/-) and (+/-) mice, which Applicant asserts to be an indication of and/or associated with retinal degeneration. This issue is relevant to the maintained written description rejection regarding the specification does not provide any information pertaining to the *structure-function relationship* of any native PRO224 polypeptide encoded by a mammalian gene.

***Conclusion***

8. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Primary Examiner
Art Unit 1632